FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC

DRUGS ADVISORY COMMITTEE

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MEETING

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FRIDAY,

JULY 27, 2001

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The Advisory Committee met in the Versailles Rooms, Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Mark E. Molitch, M.D., Acting Chairman, presiding.

PRESENT:

MARK MOLITCH, M.D., Acting Chairman

THOMAS A. AOKI, M.D., Member

DEBORAH GRADY, M.D., M.P.H., Member

WILLIAM V. TAMBORLANE, M.D., Member

ALLAN R. SAMPSON, Ph.D., Member

PRESENT (Continued):

LYNNE L. LEVITSKY, M.D., Member

MARIE C. GELATO, M.D., Ph.D., Member

KATHLEEN REEDY, Executive Secretary

ROBERT A. KREISBERG, M.D., Consultant

ERIC S. HOLMBOE, M.D., Ph.D., Rick Management Consultant

JODY L. PELOSI, F.N.P., Ph.D., Consumer Representative

HENRY G. BONE, III, M.D., Guest

BRUCE V. STADEL, M.D., M.P.H., FDA

BRUCE S. SCHNEIDER, M.D., FDA

GEMMA KUIJPERS, Ph.D., FDA

DAVID G. ORLOFF, M.D., FDA

JOHN JENKINS, FDA

C-O-N-T-E-N-T-S

PAGE

Introductions 4

Conflict of Interest Statement 7

Opening Statement, David G. Orloff, M.D. 10

Company Presentation, Eli Lilly:

Introduction, Jennifer L. Stotka, M.D. . . 12
History, Robert Lindsay, M.D., Ph.D.. . . 18
Nonclinical Overview, John L. Vahle, D.V.M. 27
Clinical Efficacy, Bruce H. Mitlak, M.D. . 39
Clinical Safety, Gregory A. Gaich, M.D. . 58
Summary and Conclusion, Bruce H. Mitlak, M.D. 80

FDA Presentation:

Preclinical Studies, Gemma Kuijpers, Ph.D. 135
Efficacy, Bruce S. Schneider, M.D. . . . 149
Safety, Bruce V. Stadel, M.D. 168

Public Comment:

Dr. Donald White 206
Deborah Zeldou 208
Dr. Peter Lurie 212

Charge to the Committee, David G. Orloff, M.D. 221

Advisory Committee Discussion 226

Closing Remarks, David G. Orloff, M.D. 329

P-R-O-C-E-E-D-I-N-G-S

(8:08 a.m.)

ACTING CHAIRMAN MOLITCH: Good morning. My name is Mark Molitch. I'm the acting chair this morning. This is the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

Today we're going to be discussing NDA 21-13 -- I'm sorry -- 318, Forteo, teriparatide injection or recombinant DNA origin. The presenters will be Eli Lilly and Company and the FDA.

We'll begin by introducing members of the table up front.

May I remind everybody that the microphones are activated by pressing on the right to speak, and after you've spoken, please then turn off the microphone to decrease the ambient noise in the room.

And we'll start on the left with Dr. Holmboe.

DR. HOLMBOE: Hi. My name is Eric Holmboe. I'm a general intern from Yale University serving as a consultant today.

DR. PELOSI: I'm Jody Pelosi. I'm an oncology nurse practitioner at the Phoenix Indian Medical Center, and I'm here as the consumer rep.

DR. AOKI: I'm Tom Aoki from the University of California, Davis, in Sacramento, California.

DR. LEVITSKY: I'm Lynne Levitsky. I'm Chief of the Pediatric Endocrine Unit at Mass. General Hospital in Boston.

DR. TAMBORLANE: I'm Bill Tamborlane, Chief of pediatric endocrinology in the Pediatric Pharmacology Research Unit, Yale University.

DR. GELATO: I'm Marie Gelato. I'm a professor of medicine and an endocrinologist at SUNY, Stony Brook.

DR. KREISBERG: Bob Kreisberg from Mobile, Alabama.

MS. REEDY: Kathleen Reedy, Executive Secretary of the Endocrinologic and Metabolic Drugs Advisory Committee, CDER.

DR. GRADY: I'm Deborah Grady. I'm a professor of medicine and epidemiology from the

University of California in San Francisco.

DR. SAMPSON: I'm Allan Sampson. I'm professor of statistics, University of Pittsburgh.

DR. BONE: I'm Henry Bone, Director of the Michigan Bone and Mineral Clinical in Detroit, Michigan.

DR. STADEL: Bruce Stadel, Medical Officer in the Division of Metabolism, Endocrine Drug Products.

DR. SCHNEIDER: Bruce Schneider, Medical Officer, Division of Metabolic and Endocrine Drug Products, CDER, FDA.

DR. KUIJPERS: Gemma Kuijpers, pharmacology reviewer at the Division of Metabolic and Endocrine Drug Products, FDA.

DR. ORLOFF: I'm Dr. David Orloff, Director of the Division of Metabolic and Endocrine Drug Products at CDER.

MR. JENKINS: And I'm John Jenkins. I'm the Director of the Office of Drug Evaluation II in CDER at FDA.

ACTING CHAIRMAN MOLITCH: Thank you,

everybody.

Kathleen Reedy will now read the meeting statement.

MS. REEDY: The conflict of interest statement for Endocrinologic and Metabolic Drugs Advisory Committee, July 27th, 2001, considering Lilly's Forteo.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 United States Code 208(b), a fully waiver has been granted to Drs. Mark Molitch, Barbara Lukert and William Tamborlane. A copy of the waiver statements may be obtained by

submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Deborah Grady, Robert Kreisberg, Barbara Lukert, Lynne Levitsky, and William Tamborlane have interests which do not constitute a financial interest within the meaning of 18 United States Code 208(a), but which could create the appearance of a conflict.

The agency has determined notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Dr. Grady, Dr. Kreisberg, Dr. Lukert, Dr. Levitsky, and Dr. Tamborlane may participate fully in today's discussions.

With respect to the FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Henry Bone would like to disclose for the record that he was an investigator on a Phase 3 study of Raloxiphene Evista (phonetic), one of the competing products to Forteo, from 1994 to 1999. Dr. Bone has participated as an investigator in several clinical trials of Alendronate and other competing product to Forteo, some of which are still current. He's also acted as a consultant to Merck.

In addition, Dr. Bone's clinic has received an unrestricted educational grant from Novartis. He has given lectures sponsored by Merck and Novartis.

Lastly, Dr. Bone is an officer of the Michigan Consortium for Osteoporosis, which has received supplementary support from Merck and Procter and Gable.

Dr. Bone receives no salary from the Michigan Consortium for Osteoporosis, but is reimbursed for his expenses.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest,

the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

I mentioned Dr. Barbara Lukert, who was not able to be with us today.

ACTING CHAIRMAN MOLITCH: Thank you, Ms. Reedy.

We'll now have an opening statement from Dr. Orloff.

DR. ORLOFF: Good morning. I want to extend my own welcome to the committee and thank you in advance for the service to the agency and to the drug regulatory process.

I'm basically going to read a statement that I read yesterday since there's a new audience, a new sponsor, as well as additional members of the Advisory Committee.

The Advisory Committee process is an

important aspect of FDA's review and regulatory decision making for new drugs, affording an opportunity for us to hear from experts in the field, from members of the public, as well as from the sponsor on the subject application.

At the outset, it should be understood by all in attendance that we, the agency, enter into this meeting without an established course of regulatory action. We are here to engage in a discussion between the committee and FDA and the sponsor on the scientific merits of the investigations, clinical and otherwise, of this drug and of the ramifications of the resultant data for a decision regarding marketing of the product for the proposed indications.

I want to remind everybody that the tone and outcomes of the deliberations today and the opinions expressed by the committee, as well as those expressed by the presenters for FDA, do not represent final agency stance on the application. Regulatory action will come only after further review, internal discussion, and clearly discussion with the sponsor.

So, again, as Director of the division

that is responsible for review and regulatory action on this product, I want to thank you for being here, welcome you. I'll have further remarks later when I charge the committee after the sponsor's and FDA presentations.

And I'll turn it back over to Dr. Molitch. Thank you.

ACTING CHAIRMAN MOLITCH: Thank you, Dr. Orloff.

The company, Eli Lilly, will now give their presentation. They've requested that we hold questions for various speakers until the end of their presentation, and then at that point they'll be open for discussion amongst the members of the panel.

So we'll start with Dr. Stotka, who is the Executive Director of U.S. Regulatory Affairs of Lilly.

DR. STOTKA: Slides on, please.

Good morning. My name is Jen Stotka. I'm a physician and the Executive Director of U.S. Regulatory Affairs for Eli Lilly & Company.

On behalf of Lilly, I thank you for the

opportunity to discuss teriparatide, which we will also refer to as recombinant human PTH 1 to 34.

The proposed trade name for teriparatide is Forteo.

The indication for which we are currently seeking approval is the treatment of osteoporosis in post menopausal women and in men.

The advantages and safety profile of this new therapy will be highlighted in subsequent presentation today. The extensive contents of this application meet or exceed all expectations contained in applicable FDA and ICH guidelines, and our clinical trials were conducted with advisement from and agreement with the FDA's Division of Metabolic and Endocrine Drug Products.

Today we will provide data that support the position that teriparatide is the first clinically useful agent in a new class of osteoporosis therapies. These new drugs are bone formation agents in contrast to the anti-resorptives currently on the market, and it will provide an important new choice for the treatment of osteoporosis in post menopausal women and

in men.

Comprehensive information from clinical trials enrolling over 2,800 women and men in 20 countries was submitted to the FDA as a new drug application in November of 2000. Our clinical evaluation of teriparatide began shortly after our initial IND filing in August 1995. The clinical development plan was formulated following input from a number of external consultants and the FDA.

Key points of the FDA's draft guidelines on the clinical development of osteoporosis drugs published in April of 1994 were taken into consideration when we designed our clinical program.

The pivotal study in post menopausal women with osteoporosis began in December of 1996, while our pivotal study in men with osteoporosis began in July of '97.

In December 1998, Lilly reported to the FDA an unexpected finding of osteosarcoma in a two-year rat carcinogenicity study. We informed the FDA of our decision to voluntarily stop all ongoing trials with teriparatide while this nonclinical finding was

evaluated further.

In April 1999, Lilly submitted the recommendations of an external oncology advisory board to the FDA. This advisory board was convened to assist in the evaluation of the nonclinical osteosarcoma finding.

Lilly and the FDA discussed the appropriate follow-up for patients.

Shortly thereafter an observational study was implemented to continue to collect safety information in all patients previously enrolled in our Phase 3 program of teriparatide.

In July 1999, Lilly, the FDA, and external experts from our oncology advisory board participated in a meeting held at the FDA's request to discuss this nonclinical osteosarcoma finding. In September 1999, we met with the FDA to discuss preliminary safety and efficacy results of our pivotal Phase 3 study and to propose the content for an NDA.

Agreement was obtained from the FDA that the NDA package was adequate to support submission of teriparatide as a new agent for the treatment of

osteoporosis in post menopausal women.

In July of 2000, Lilly and the FDA held a pre-NDA meeting. Agreement was reached with the FDA that the data with teriparatide also appeared to be adequate to support submission of teriparatide as a new agent for the treatment of osteoporosis in men.

The NDA was submitted in November of 2000. The requisite four-month safety update was submitted in March of 2001, and today we will demonstrate that the data submitted in our NDA meet or exceed the burden of proof for efficacy and safety.

Our presentations today encompass a number of scientific and regulatory matters. In fact, we will address all questions that the FDA has asked you to consider regarding the mechanism of action of teriparatide, efficacy in women and men, bone quality, and overall safety.

We will also review the rationale for the selection of our 20 microgram dose, and we will provide you with an assessment of the overall benefit-risk profile.

We will follow this agenda. First, Dr.

Robert Lindsay, Professor of Clinical Medicine at Columbia University, College of Physicians and Surgeons, Chief of Internal Medicine at Helen Hayes Hospital, and past president of the National Osteoporosis Foundation, will discuss history, mechanism of action, and the unmet medical need.

Following him will be presentations by Lilly scientist:

Dr. John Vahle, veterinary pathologist, will cover nonclinical pharmacology and toxicology.

He will be followed by Dr. Bruce Mitlak, Medical Director for the teriparatide team, who will review the clinical efficacy data.

Next Dr. Gregory Gaich, senior clinical research physician, will present an overview of the safety profile of teriparatide.

And finally, Dr. Mitlak will provide the overall benefit-risk summation in our conclusions.

We look forward to a full discussion of the issues raised. Dr. Mitlak will facilitate Lilly's response during the discussion period.

Additionally, we have a number of our key

scientific staff and external experts available here today to help respond to your questions.

In fact, we wish to thank the following experts for working with us and for being here today to assist with your deliberation: Dr. Adamson, Bellizikan, Chabner, Lindsay, Neer, Potts, and Stewart.

We ask for your active consideration to approve teriparatide for the treatment of osteoporosis in post menopausal women and in men. We believe the documentation provided will support such action, and we look forward to a mutually productive session.

I now have the pleasure of introducing Dr. Robert Lindsay for the scientific overview.

DR. LINDSAY: Thank you very much, Dr. Stotka.

Mr. Chairman, ladies and gentlemen, members of the advisory panel, it is a considerable pleasure for me today to introduce to you the topic of parathyroid hormone, an agent that my group has had considerable interest in for the past 15 years.

To set the stage, I shall briefly review

the history, mechanism of action, and clinical need for recombinant 1 to 34 human parathyroid hormone as a treatment of osteoporosis in both women and men. Much of the data I will use comes from our specialized center of research funded by the National Institutes of Health.

The parathyroid glands were originally identified by Sandstrom some 121 years ago, and for the next 25 years, their function was hotly debated.

In 1906, Erdheim produced evidence that the parathyroid glands were intimately linked in calcium homeostasis, and in 1925, Collip, working with Eli Lilly Company, prepared a purified, stable extract that was clinically active, and was subsequently marketed.

That parathyroid hormone can be anabolic. It's not new nor novel. In 1929, Orb (phonetic) working with Fuller Albright, first demonstrated the anabolic effect by injecting the extract prepared by Collip into rodents, a finding confirmed some three years later by Hans Selye.

These experiments were largely forgotten

until the early 1970s when Nile, Jerry Aerbach, John Potts first sequenced and synthesized the 1 to 34 of minor terminals of parathyroid hormone and subsequently the complete peptide.

This allowed sufficient purified peptide to be synthesized to more fully evaluate its pharmacological profile. Today, of course, 1 to 34 human parathyroid hormone is reduced by recombinant technology rather than by protein synthesis.

Initial experiments confirm the anabolic action in rodents and subsequently in other species, including dogs and nonhuman primates.

The first human experiments were initiated in the 1970s by the late John Parsons in collaboration with John Potts, Bob Neer, Jonathan Reeve and Pierre Munier (phonetic) and others. These studies confirmed that parathyroid hormone could exert an anabolic effect on the human skeleton, first published in 1980.

During the 1990s, several relatively small, controlled clinical trials have been completed. These trials all showed that one to 1 to 34 human parathyroid hormone could produce marked increases in

bone mass, particularly in the lumbar spine, but also in the total hip.

The doses that were used varied from 400 to 800 units, international units, in the original concept, roughly equivalent to the dosage used in the Phase 3 studies about which you will hear later.

These data are exemplified by data from our own group published by Felecia Cosman (phonetic) and colleagues in 2001 that demonstrate an increase in vertebral bone mass over a three-year period of approximately 13 percent in an experiment in which parathyroid hormone was delivered by daily subcutaneous injection on top of already coexisting hormone replacement therapy. These data show the increase in bone mass in the spine.

In addition to these changes in the spine, there was also a significant increase in bone mass in the hip, again, over a three-year period, somewhat less than in the spine, but amounting to slightly more than four percent.

Similar data have been published using parathyroid hormone by itself.

Although this study was not powered to detect reductions in fracture, we were able to demonstrate statistically significant reductions in vertebral fracture during the three years of the study primarily because we actually saw no fractures in the PTH treated group.

The effects of PTH on bone mass occur by mechanisms that differ markedly from currently available anti-resorptive agents. About a year or so ago, Tony Hodgeman (phonetic) published data on iliac crest bone biopsies obtained one month after starting parathyroid hormone. After only four weeks of therapy, Hodgeman demonstrated an increase in osteoid surface, an increase in the surface of bone covered by osteoblasts, and a dramatic threefold increase in bone formation rate.

Later this year at the American Society of Bone and Mineral Research, we will present further data from these biopsies that demonstrate that those increases in bone formation occur not only in sites of prior resorption, but also on inactive surfaces, and that they occur in both the trabecular bone and osteo

bone and periostea bone.

Our biochemical data confirm these histomorphometric responses. This slide demonstrates the increase in osteocalcin, a marker of bone formation, and an NTL (phonetic) peptide, a marker of bone resorption during the early course of treatment with parathyroid hormone.

You can see that osteocalcin increases dramatically and quickly, such that by one month of treatment there is about a 55 percent increase. There is a slower lag in the increase in NTX (phonetic), but by six months the full pharmacological effects of parathyroid hormone are evident. Parathyroid hormone stimulates both bone formation and also bone remodeling.

The consequence of these phenomena is not only an increase in bone mass, but an improvement in the structure of the skeleton with normal amellor (phonetic) bone being laid down.

Data currently in press from the studies that we have conducted in collaboration with John Bellizikan demonstrate that in both men and in women

there is improvement in the connections among trabeculari (phonetic) within a bone.

These trabecular connections are best seen in a single patient slide shown in the next slide in which we have compared a biopsy from a 64 year old woman before parathyroid hormone, with an iliac crest biopsy from the opposite side in the same woman approximately two and a half years after parathyroid treatment.

It is clear that not only is there more bone present in the slide on the right, but also there are increases in the numbers of trabeculari that are present.

In addition to the numbers of trabeculari and the proved connectivity shown here, there is also rather surprisingly to us initially an increase in cortical thickness shown here and shown here. These improvements in cortical thickness differentiate the use of parathyroid hormone as an anabolic agent when delivered by subcutaneous injection from the disease primary hyperthyroidism.

Currently available treatments for

osteoporosis are clearly effective. These agents work by reducing bone remodeling and allay bone loss. However, many patients remain at significant fracture risk.

Osteoporosis -- I beg your pardon. Remain at significant fracture risk.

Next slide.

The reductions in fracture risk that one sees with anti-resorptive agents amount to some 35 to 55 percent over a three-year period in patients with vertebral fracture. In addition, these agents are unable to restore bone matrix or architecture in the way in which we have demonstrated with parathyroid hormone.

We believe, therefore, that an unmet medical need continues to persist. Osteoporosis is not a trivial disease. We are well accustomed to the concept that hip fracture is associated not only with increased morbidity, but also with increased mortality.

Data published from the fracture intervention trial by Jane Collie (phonetic) and

colleagues just last year demonstrated one feature of the disease, and that is that not only is hip fracture associated with an age adjusted increase in the relative risk of mortality, but that spine fractures are also, and that there is almost a linear correlation between the number of spine fractures that present and also the increase in mortality.

Data that we published in the Journal of the American Medical Association earlier this year demonstrates that when a patient presents with a new vertebral fracture, he or she will have a 20 percent increase in the likelihood of yet another fracture within a single year.

Next slide.

Unlike current agents, parathyroid hormone stimulates new bone formation and remodeling, rapidly increases bone mass, and by this unique mechanism of action, restores skeletal architecture.

In conclusion, therefore, ladies and gentlemen, teriparatide or recombinant human parathyroid hormone 1 to 34, as will be shown in the following presentations, reduces fracture risk

significantly, and as I have demonstrated, works by a unique mechanism of action that I believe changes the paradigm for the treatment of osteoporosis and offers benefits to patients with osteoporosis that cannot be seen with current therapeutic options.

It's now my pleasure to introduce Dr. Vahle from the Eli Lilly Company, who will review the preclinical data.

DR. VAHLE: Thank you, Dr. Lindsay.

My name is John Vahle, and I am a veterinary pathologist with the teriparatide team.

I will briefly review the key findings from the animal studies conducted with teriparatide. Overall our nonclinical pharmacology and safety studies meet or exceed all worldwide regulatory guidances.

First, I'll describe the skeletal effects of teriparatide in our most relevant animal model, the mature ovariectomized Cynomolgus monkey.

Then I'll review the nonclinical safety data by briefly reviewing key findings from the animal toxicity studies.

And I will conclude by presenting the results from the two-year rat study previously mentioned by Dr. Stotka in which osteosarcomas were observed.

In monkeys, teriparatide increases bone mass and improves skeletal microarchitecture. These high resolution CT scans of the fifth lumbar vertebra were obtained in an 18-month skeletal pharmacology study in which ovariectomized monkeys were given teriparatide for up to 18 months and illustrate increased trabecular bone from a monkey given five micrograms per kilogram per day as compared to that from an ovariectomized control monkey.

Histomorphometry of the vertebra show that teriparatide stimulated new bone formation on both cortical as well as trabecular surfaces, resulting in increases in trabecular number, in connectivity, as well as increases in cortical area.

These improvements in skeletal architecture are not achieved with anti-resorptives. Most importantly, these effects on bone mass and microarchitecture result in increases in bone strength

at both the vertebra as well as the hip.

There have been concerns that the substantial increases in trabecular bone produced by parathyroid hormone might occur at the expense of cortical bone. However, in this long-term monkey study, there were no adverse effects on cortical bone based on the following data.

Cortical bone mass was maintained at the mid-shaft of long bones, such as the radius, humerus and femur. Histomorphometry at these predominantly cortical locations revealed the anticipated teriparatide mediated enhancement of cortical remodeling.

A natural manifestation of this process was an increase in endocortical porosity which was accompanied by enlargement of cortical area and thickness.

There were no deleterious effects on cortical bone strength, and in fact, the net effect was that there is increased resistance to fracture at the mid-shaft humerus and radius.

I will now briefly summarize some of the

key findings from the nonclinical safety studies. In the rat and monkey toxicity studies which supported clinical development, the important effects were primarily related to the known pharmacology of parathyroid hormone on either bone or mineral ion metabolism.

The most important effect in the monkey was the histologic observation of interstitial basophilia in the renal medulla. This effect was closely related to the magnitude and duration of hypercalcemia and did not appear to have an impact on renal function.

In contrast, renal histologic changes did not occur in the 18-month pharmacology study I previously described. As will be shown on the following slide, difference in these two monkey models account for the differing effects on renal histology.

In the toxicity studies in which renal changes occurred, the animals were young, immature, intact male and female monkeys who received a dietary calcium intake approximately six times higher than that of a post menopausal woman receiving calcium

supplementation.

In the pharmacology study, there were no renal alterations even at doses that cause similar changes in the toxicity studies. The monkeys in this model are mature, ovariectomized females with a daily calcium intake approximately two to three times higher than a supplemented post menopausal woman.

Therefore, the lack of renal effects in this more clinical relevant model in which monkeys were treated for up to 18 months at doses which provided exposures up to eightfold that of a human receiving a 20 microgram dose provide substantial evidence that the histologic alterations in the toxicity studies do not represent a substantial safety concern.

In addition to the effects in the chronic toxicity studies just described, other important findings included a lack of genotoxicity and a full battery of in vitro and in vivo assays that meat global regulatory standards, and the findings in the two-year rat study.

In the next few minutes I'll review the

primary findings from this study, which include exaggerated increases in bone mass, bone proliferative lesions, including osteosarcoma.

Importantly, there was no increase in the incidence of tumors in any other tissue or organ. As is standard practice in these types of studies, treatment with teriparatide was initiated in skeletally immature rats six to eight weeks of age and was continued for two years, which constitutes near lifetime treatment.

These high resolution CT images of the proximal femur illustrate the dramatic effects on bone mass that occurred in this two-year study.

This image from a control rat shows a normal pattern of cortical bone, trabecular bone, and intervening marrow space. In all teriparatide treated groups, there is a marked increase in both cortical bone as well as trabecular bone. In fact, the effect is so profound that it leads to near obliteration of the marrow space.

In terms of serum concentrations of teriparatide, these doses provided exposures that were

three, 20, and 58 times that patients given a 20 microgram dose. These images and the supporting quantitative data show that even the lowest dose in rats results in exaggerated effects on bone mass that do not occur in patients, as illustrate in the following slide.

These figures compare the effects on bone mass in the two-year rat study to those observed in osteoporotic women and in monkeys. In the left panel are data from the diaphysis, primarily cortical bone site. On the right, the vertebra, a primarily trabecular bone site. On the Y axis is bone mineral content, a measure of bone mass expressed in these figures as a percent above control values. On the X axis is systemic exposure to teriparatide expressed as area under the curve or AUC.

The data points are from women with osteoporosis given the high dose, 40 micrograms, in the Phase 3 trial; rats given the low dose, five micrograms per kilogram, in the two-year rat study; and monkeys given the high dose of five micrograms per kilogram in the 18-month pharmacology study.

These data sets were selected because they are the most closely comparable in terms of duration of treatment, ranging from 18 to 24 months, systemic exposures to teriparatide, and the skeletal locations examined, and they show that over a comparable range of exposures, osteoporotic women and monkeys have similar increases in bone mass.

In contrast, rats have marked increases in bone mass at both cortical as well as trabecular sites.

It is also important to note that this increase in the rat in above peak bone mass for a normal rat, while the value shown for women is the percent above a woman with osteoporosis. So that although women who received teriparatide treatment have increases in bone mass, their bone mass does not exceed peak values for normal, healthy women.

In addition to the exaggerated increases in bone mass, the other important finding in this study was the occurrence of bone proliferative lesions. The majority of these lesions were osteosarcomas that occurred with a dose dependent

incidence in all dose groups in both males and females.

There were 60 rats per sex per group in this study, and at the high dose of 75 micrograms per kilogram, the incidence reached approximately 50 percent.

These lesions occurred at multiple sites in both the axial and appendicular skeleton, and metastasis to soft tissue occurred in approximately one third of the rats with osteosarcoma.

In addition, there was a low incidence of benign proliferative lesions of bone.

In addition to the profound increases in bone mass and the bone proliferative lesions, including osteosarcoma I've just described, there was no increase in the incidence of tumors and other tissues, including the mammary gland and the kidney, tissues with high concentrations of PTH receptors.

Based on the initial observation of bone tumors in rats, Lilly made the voluntary decision to stop treatment of patients in the Phase 3 trials while the findings in the rats could be studied. We

extensively reviewed these findings with a variety of internal and external experts, including the formation of an external oncology advisory board composed of oncologists, epidemiologists, and pathologists.

After considering data from the rat study and the relevant scientific literature, the advisory panel reached the conclusion that in spite of not identifying a no effect level, the findings from the two-year rat study are not likely to be predictive of an increased risk of osteosarcoma in patients with osteoporosis who were treated with teriparatide.

A variety of factors have been considered in assessing the predictive potential of the findings from the rat model. First, there are important differences between the rat model and the intended clinical use which account for the extreme effects seen in the rodent skeleton.

First, rats are exposed for a relatively long proportion of their lifetime, which is in contrast to patients who would receive treatment for a relatively short proportion, approximately two to three percent.

In addition, there are distinct differences in skeletal biology between rats and humans. For example, rats continue to have longitudinal skeletal growth throughout life, and their growth plates remain open, which is in contrast to humans whose growth plates close at the time of adolescence.

Also, rats lack the mechanism to replace old cortical bone with new cortical bone, a process known as osteonal remodeling.

Importantly, teriparatide is not genotoxic, and it is known that rodent carcinogenicity assays are not always predictive for non-genotoxic agents. The exaggerated effects, skeletal responses observed in the study were mediated by the interaction of teriparatide with the PTH receptor on the osteoblast, and in two-year rat studies with a variety of agents, it has been shown that continual hormonal stimulation such as this can induce tumors in rats which are not relevant to humans.

For example, proton pump inhibitors, such as omeprazole cause gastric carcinoids in rats due to

chronic increases in gastrin levels. However, similar neoplastic responses have not occurred in humans treated with omeprazole despite the fact that they also have chronic increases in gastrin levels.

Because of the differences in rats and humans, and there are questions about the predictivity of the rat findings, it is important to consider the data from other species. In terms of other animal data, the most relevant is a lack of bone lesions in an 18-month pharmacology study in which 80 skeletally mature ovariectomized animals were given teriparatide for up to 18 months at exposures up to eightfold greater than women receiving a 20 microgram dose.

We also carefully reviewed the literature on human hyperparathyroidism, and while we recognize important temporal differences between hyperparathyroidism and the daily administration of teriparatide, there is no evidence of an increased risk of bone cancer in patients with hyperparathyroidism, despite the fact that there is chronic stimulation of the osteoblast in new bone formation in both cases.

In summary, the nonclinical evaluation of teriparatide has been rigorous, and the following conclusions can be made. The pharmacology studies clearly show that teriparatide stimulates new bone formation resulting in increases in bone mass, improvements in skeletal microarchitecture, and increases in bone strength while maintaining cortical bone quality.

In particular, these improvements in skeletal microarchitecture are not achieved with anti-resorptive.

In animal toxicity studies, effects were primarily related to the known activity of PTH or related peptides on bone or mineral ion metabolism, and the findings do not represent important clinical safety concerns.

And, finally, a thorough review of the two-year rat study in the relevant scientific literature, we believe that the osteosarcoma findings are not predictive of an increased risk of bone tumors in osteoporosis patients treated with teriparatide.

This concludes the nonclinical data

review. It's now my pleasure to introduce Dr. Bruce Mitlak, Medical Director, who will review the clinical efficacy data.

DR. MITLAK: Thank you, Dr. Vahle.

Good morning, Mr. Chairman, committee members. My name is Bruce Mitlak. I'm a physician and Medical Director on the teriparatide team.

I have the pleasure of reviewing the evidence with you that teriparatide treatment increases bone mineral density, improves bone architecture, and prevents fractures in patients with osteoporosis.

The clinical program included 25 trials that enrolled more than 2,800 women and men worldwide. The study codes and titles for the fully enrolled Phase 3 programs and our ongoing observational follow-up study are shown on this slide. I will use these codes to identify the studies in my presentation.

As I will describe this morning, the pivotal placebo controlled study in women was GHAC, and the pivotal study in men was GHAJ. Studies GHAF and GHAH are supportive studies which are included in

your briefing document, but will not be included in my presentation this morning.

Study GHBJ is the ongoing observational follow-up study in which prior Phase 3 patients are currently being followed.

This diagram includes the two pivotal clinical studies that I will present this morning. Study GHAC enrolled 1,637 women with osteoporosis to evaluate the effect of teriparatide treatment on the risk of fracture.

Study GHAJ enrolled 437 men with osteoporosis to evaluate the effective of teriparatide on bone mineral density.

In December 1998, we voluntarily stopped these studies and asked patients to complete an early discontinuation visit. This action was taken to allow further evaluation of the finding of osteosarcoma in a concurrent long-term toxicology study as just described by Dr. Vahle.

Women participated in Study GHAC for a median of 21 months and men in GHAJ for a median of 12 months at the time of the respectively study

closeouts.

We created an observational follow-up study called GHBJ. The primary purpose of this study was to collect safety information and to maintain contact between the study sites and our study patients.

All patients who had been enrolled in these studies, as well as our other Phase 3 studies were invited to participate. Now I will first focus on results from Study GHAC.

Study GHAC, the pivotal study in women, enrolled 1,637 women. It is a prospective, randomized double blind trial that was performed in 99 sites at 17 countries. Post menopausal women who were at least five years post menopausal and who had a radiographically confirmed vertebral fracture were eligible to participate.

The primary endpoint in this study was the proportion of women with one or more new vertebral fractures. All women self-administered a once daily subcutaneous injection that included either teriparatide, 20 micrograms, teriparatide, 40

micrograms, or placebo, and all women were provided a supplement that included 1,000 milligrams of calcium and 400 to 1,200 units of Vitamin D.

The baseline characteristics for women in the study are shown by treatment group, and in this presentation the placebo group will be shown in white, the teriparatide 20 group in yellow, and the teriparatide 40 group in blue.

The groups were balanced for the characteristics shown, as well as for other factors which could affect the risk of fracture. The mean age was 69 to 70. There was a slightly greater proportion of women greater than 70 years of age in the two teriparatide groups compared with the placebo group.

The mean number of years since menopause was 21 to 22 years. Prior treatment for osteoporosis was reported by 13 to 16 percent of the women, but no treatment was permitted for between six and 24 months prior to the beginning of the study, depending on the specific treatment.

Baseline spine bone mineral density expressed in standardized units was approximately 820

milligrams per centimeter squared, corresponding to a T-score of about minus 2.6, and as shown, approximately 60 percent of these women had two or more prevalent fractures at the beginning of the study.

Because of early closure, women completed different lengths of time in the study. This panel shows the number of women who completed the specified months on the X axis. Because women were asked to suspend study medication and then were scheduled for their final visit, exposure to study medication was on average eight weeks shorter than the duration shown on this slide.

You can see that the duration of observation was similar across treatment groups. Relatively few women in any group left the study before 18 months. The maximum duration between baseline and final radiograph for a patient was 27 months, and the median was 21 months.

Eighty-one percent of the women in this study had an adequate baseline and follow-up radiograph.

This figure shows the scale used to grade both baseline and incident vertebral fractures in this study. Vertebral bodies that are either normal or a fracture that is crushed in the anterior, mid or posterior part of the vertebral bodies are shown.

Radiologists who were blinded to treatment assignment called vertebrae either normal or reported to us the presence of a mild, moderate or severe fracture using this scale as specified in the protocol. While this is a semi-quantitative scale, these grades correspond to approximately a 20, 25, or 40 percent or greater loss of height of the vertebral body.

In this study, a fracture was reported if a vertebrae had a score of zero at baseline and was found to have a score of one, two, or three at follow-up. Over the 21 months of the study, 105 women were found to have one or more new vertebral fractures.

Results for the primary efficacy endpoint are summarized on this slide. Let me review the format which will be used also on the subsequent two slides.

The number of women with one or more new fractures in each group is shown on the respective treatment bar. The height of the bar corresponds to the proportion of women within each group with a fracture. The relative risk in 95 percent confidence intervals are shown for each comparison to placebo, and all p values refer to comparisons with placebo.

Teriparatide reduces the risk of vertebral fractures. In women assigned to treatment with teriparatide, the relative risk for fractures were .35 and .31, corresponding to a highly statistically significant 65 and 69 percent reduction in the likelihood of a fracture. The absolute risk of fracture was reduced from approximately 14 percent to five percent and four percent.

Additional analyses were performed to evaluate the effective of treatment on more severe fractures in this study. This figure shows the results for women who had one or more vertebral fractures that were at least of moderate severity.

While ten percent of women assigned to placebo had fractures that were moderate or severe in

degree, only one and two percent of women assigned to treatment with teriparatide had such a fracture. The relative risk of .1 and .22 corresponds to a 90 and 78 percent reduction in the risk of having a moderate and severe fracture.

In this study, we found that regardless of treatment, women with more severe fractures were more likely to report back pain or to suffer height loss.

This panel shows results for women who had two or more new vertebral fractures during the study. The relative risk for multiple vertebral fractures was .23 and .14, corresponding to a 77 and 86 percent reduction in the risk of having two or more new vertebral fractures

Teriparatide treatment reduces the risk of overall nonvertebral fragility fractures. This figure shows the proportion of women who reported one or more nonvertebral fragility fractures both overall and by specific skeletal site.

As specified by the protocol, site investigators determined whether a fracture was associated with excess trauma, such an association

with an automobile accident or fall greater than a standing height. Fifty-eight women had fractures that did not result from excess trauma, and these were considered fragility fractures.

Teriparatide treatment significantly reduced the risk of nonvertebral fragility fractures. The relative risk of .47 and .46 correspond to a 53 and 54 percent reduction in the risk of fracture in each group compared with placebo.

And while there were a small number of women with fractures at any specific skeletal site, the figure shows that there was a similar or lower proportion of teriparatide treated women with a fracture at each site compared with placebo, including the radius, which I will return to in a few minutes.

This analysis of the same data for the placebo group in white, the teriparatide 20 group in yellow and 40 group in blue now shows the data as time to first event, and it demonstrates that the effective treatment on the risk of nonvertebral fracture became progressively apparent after about nine months of treatment.

It also shows that at no time during the study was there evidence for an increase in risk for these fractures.

Teriparatide treatment increases lumbar spine bone mineral density. Lumbar spine bone density increased significantly with teriparatide treatment at each visit where it was assessed, including the first visit at three months, where nearly a four percent increment in bone density had already occurred.

At endpoint, the difference in bone mineral density between the 20 microgram group and placebo was nine percent and between the 40 microgram group and placebo was 13 percent.

Ninety-six percent of women in the study assigned to teriparatide 20 micrograms had an increase in bone mineral density. These increases in bone density were associated with rapid increases in biochemical markers of bone formation and secondarily bone resorption.

Teriparatide treatment increases hip bone mineral density. Total hip bone mineral density was measured in approximately one half of the women in the

study at a subset of study sites, and femoral neck bone density was measured in all women.

At endpoint, total hip bone mineral density decreased by about one percent, and in contrast, increased in both of the teriparatide groups.

The mean difference between the teriparatide groups and placebo at endpoint was 3.6 percent and 4.6 percent. Each comparison was statistically significant.

At the femoral neck compared with placebo, the increase in bone mineral density at endpoint was four percent and six percent. Other hip sites were also significantly increased by teriparatide treatment.

Ultra distal and distal radius bone mineral density was measured in about 450 women. At the ultra distal radius, bone density declined slightly in the placebo group, but did not change significantly in any group, nor were there differences between groups.

At the radial shaft bone mineral density

decreased about one percent in women assigned to placebo. The difference between the treatment group and placebo was one percent in the women assigned to treatment with 20 micrograms and two percent in women treated with 40 micrograms of teriparatide.

The 40 microgram group differed significantly from the placebo group. This early decrease in bone mineral density likely reflects increases in cortical bone remodeling and as demonstrated by PQCT in a subset of approximately 100 women was associated with preserved cortical thickness and evidence for periosteal new bone formation.

Importantly, it was also associated with a humerically lower number of wrist/forearm fractures in the teriparatide group, as I had previously highlighted for you.

Importantly also, teriparatide increases total body bone mineral. Total body bone mineral was measured in about 400 women at a subset of study sites. Compared with the placebo group which lost .7 percent, the increase in the 20 and 40 microgram groups were 2.6 and 3.5 percent, each comparison

statistically significant.

This confirms that the increases in spine and hip bone density are associated with a net increase in total body bone mass.

Transiliac bone biopsies were obtained from 61 women at baseline and then again at either 12 months or study closeout. This slide shows the baseline and endpoint bone biopsy from one patient in the 20 microgram group and one patient in the 40 microgram group who had spine bone density responses similar to the mean for their respective treatment groups.

The green stain shows calcified elements, including both the inner and outer cortical shells, as well as trabecular bone.

Also apparent is marrow space and a small amount of extraosteo soft tissue. Trabecular bone volume, TBV, is indicated below each biopsy.

Dr. Eric Erickson, the reader for these biopsies, determined in blinded fashion that there was no evidence for woven bone, abnormal mineralization, cellular proliferation, or abnormal architecture in

these biopsies.

Among the biopsies taken at 12 months, there was an increase in intra cortical remodeling in the 40 microgram group, but not the 20 microgram group. This was no longer observed in the biopsies taken at study closeout.

This remodeling transient is consistent with the results observed in the primate study and did not adversely affect biomechanical strength in the monkeys.

In addition to the favorable effects on trabecular bone volume just shown, there was significant increases or trends to increase in mineral apposition rate, wall thickness, trabecular thickness, and a measure of connectivity, connectivity of the trabeculae.

So to summarize the results from this study, teriparatide treatment was effective at preventing spine and non-spine fractures in women with osteoporosis. Treatment with teriparatide 20 and 40 micrograms reduced the risk of vertebral fractures by 65 and 69 percent; reduced the risk of nonvertebral

fragility fractures by 53 and 54 percent; increased bone mineral density at the spine and hip but not the forearm; increased total body bone mineral and had favorable effects on bone architecture.

Now I will present the results from our study in men. Study GHAJ was a prospective, randomized double blind study in men with osteoporosis performed at 34 sites in 11 countries. Four hundred thirty-seven men with osteoporosis either associated with hypogonadism or with idiopathic osteoporosis were enrolled with low bone mineral density at either the spine or the hip.

The primary endpoint of the study was change in bone mineral density at the spine. All men self-administered a once daily subcutaneous injection, again containing either teriparatide 20 micrograms, 40 micrograms, or placebo, and all were provided supplements containing 1,000 milligrams of calcium and 400 to 1,200 units of Vitamin D.

The baseline characteristics for men in the study are shown again by treatment group. The groups were well balanced for the characteristics

shown. On average men were 58 to 59 years of age. Twelve to 18 percent reported the use of other treatments for osteoporosis prior to the study, but, again, none were permitted for six to 24 months prior to randomization. Mean baseline T-scores for the spine, femoral neck, and total hip are shown by treatment group.

This figure shows the exposure in GHAJ from the time of randomization to the time of the last bone mineral density measurement. The median duration of follow-up in this study was 12 months.

For the same reason as the study in women, the actual time receiving study medication was in this case about four weeks on average less than the duration shown here.

Teriparatide treatment significantly and rapidly increased spine bone density in men. At endpoint spine bone density had increase 5.4 and 8.5 percent in the 20 and 40 microgram groups compared with placebo. The bone mineral density response was rapid, with a significant increase compared with placebo at the first measurement point in the study at

three months.

Importantly also, response in bone density was similar in men with osteoporosis associated with hypogonadism and those with idiopathic osteoporosis.

Because most men were, in fact, completing an early discontinuation visit rather than a formal 12-month visit at the 12-month time point, the data will be shown as baseline to endpoint. At endpoint total hip bone mineral density had increased .63 percent in the 20 microgram group compared with placebo, which itself had increase .54 percent. This comparison reached a p value of .074.

The mean increase between the 40 microgram group and placebo was 1.6 percent. At endpoint femoral neck bone mineral density had increased 1.2 and 2.6 percent in the 20 and 40 microgram groups compared with placebo. Each of these comparisons was statistically significant.

However, at other hip sites the comparison for the 20 microgram group was not significant.

Importantly teriparatide treatment increased total body bone mineral in men. Total body

bone mineral was measured in 254 men at a subset of study sites. At endpoint total body bone mineral had increase 1.1 and 1.3 percent in the two treatment groups compared with placebo. Each comparison was statistically significant.

So to summarize, treatment with teriparatide was effective at increasing bone mineral density in men. Treatment with teriparatide 20 micrograms and 40 micrograms increased bone mineral density at the spine and femoral neck. Total hip bone density was significantly increased only for the 40 microgram dose.

There was a significant increase in total body bone mineral for both doses.

To further evaluate the effect of gender on response to treatment, we compared the mean actual change in bone mineral density from women in Study GHAC, in men in Study GHAJ. We compared the actual change because we found, unlike percent change, the actual change was independent of baseline bone mineral density, and men in Study GHAJ started with a higher bone density than did women in Study GHAC.

As you can see, the actual change in bone mineral density for women and men for a comparable period of treatment are nearly identical.

Similarly, actual change in bone mineral density at the femoral neck for comparable period of time is identical for men and women. This is shown for men with a measurement up to the 12-month time point in the protocol.

These two panels support that gender was not an important factor in the expected response to treatment.

So to summarize, despite early study completion, both Studies GHAC and GHAJ clearly reached their specified primary endpoints.

Treatment with teriparatide 20 micrograms and 40 micrograms significantly reduced the risk of vertebral and nonvertebral fractures in both menopausal women. The reduction was similar for each dose.

Treatment rapidly and significantly increased bone density in post menopausal women and in men, and treatment improved bone microarchitecture.

That concludes this presentation. I would now like to introduce Dr. Gaich, who will review the clinical safety.

DR. GAICH: Thank you, Dr. Mitlak.

Good morning, Mr. Chairman, committee members. My name is Gregory Gaich. I'm a physician on the teriparatide team, and I am pleased to show you the data which establishes the safety and tolerability of teriparatide in the treatment of post menopausal women and men with osteoporosis.

Like the efficacy data just presented, the data that I will show you also supports the 20 microgram dose as the proposed marketed dose.

I'll review the overall safety experience, the results of the clinical and laboratory safety evaluations in our study in post menopausal women and in our follow-up study and in our study in men with osteoporosis.

I'll conclude with the results of the drug interaction and special population studies which were performed.

Our clinical investigations included 25

trials, which enrolled over 2,800 women and men, more than 1,900 of whom received teriparatide. Does of five to 100 micrograms were used in the clinical pharmacology studies, and doses of 20 and 40 micrograms were studied in our long-term Phase 3 studies. Total patient exposure to teriparatide was over 1,900 patient-years.

This slide shows the overall results of the clinical safety evaluations in the two placebo controlled Phase 3 studies combined. In this slide, the total number of patients in each dose group is shown at the top of the column, and each row shows the number and the percent of patients in each treatment group who had the listed event.

As shown in the table, the number of patients experiencing any adverse event was similar in all three treatment groups. There was a significant increase in the number of patients who discontinued due to adverse events in the 40 microgram group, but not the 20 microgram group.

The discontinuations in the 40 microgram group were primarily due to nausea.

The number of patients experienced in the teriparatide treated groups experiencing any serious adverse event, cancer, or death was similar or lower in the teriparatide treated groups compared with placebo. No osteosarcoma or other primary bone tumor occurred in any patient.

There were very few deaths in the studies, and the difference in the treatment groups was not statistically significant. None of the deaths were judged to be related to study drug by the investigator, and there were no patterns in the cause of death.

In addition, there was no difference in the morality among treatment groups in patients in older or younger age groups.

The evaluation of treatment related clinical and laboratory effects is based on the data from all of our studies. I'll focus on the data from the pivotal Phase 3 study in post menopausal women, GHAC, in which 1,637 patients were treated for up to two years.

I'll also show the data from the clinical

pharmacology studies and/or other Phase 3 studies where it provides additional information.

In Study GHAC, the adverse events in the 20 microgram group were general mild and did not lead to discontinuation from the study. Leg cramps were reported by two percent more patients in the 20 microgram group than in the placebo group, and this was statistically significant.

In the 40 microgram group, headache and nausea were significantly increased compared with placebo, but this was not observed in the 20 microgram group.

There was a numerical, although not statistically significant, increase in the incidence of nausea in the 20 microgram group, and nausea may also be treatment related at the 20 microgram dose as well as 40 microgram dose.

There was also a treatment related reduction in the incidence of new or worsened back pain in both treatment groups, and this is consistent with the reductions in vertebral fractures which Dr. Mitlak presented.

Similar significant reductions or trends in back pain were also observed in the other three phase three studies.

Next I'd like to review the results of the pharmacokinetic and safety laboratory evaluations in Study GHAC. All of the laboratory effects observed in our studies were expected based on the known pharmacology and physiology of parathyroid hormone.

This is a best fit analysis of the serum teriparatide concentrations obtained from 360 patients in Study GHAC. The solid line shows the mean teriparatide concentration following a 20 microgram dose. The hatched area shows the 25th to 75th percentile range.

The upper limit of endogenous parathyroid hormone 1 to 84 is shown in the horizontal line. The serum concentrations of teriparatide peaked at approximately 30 minutes post dose and declined rapidly thereafter, with an apparently elimination half-life of approximately 60 minutes. By three to four hours post dose, very few patients had measurable teriparatide in the serum, and there was no

accumulation of teriparatide with repeat dosing.

The average 24-hour exposure of teriparatide and endogenous PTH combined did not exceed the upper limit of normal for endogenous PTH.

Serum calcium was also measured at every visit, and we performed a similar best fit analysis on the serum calcium measurements.

This graph shows the serum calcium analysis overlaid on the pharmacokinetic analysis. The vertical axis on the left shows the teriparatide concentrations, and the vertical axis on the right shows the serum calcium concentrations. The upper limit of normal for serum calcium of 2.64 millimoles per liter or 10.5 milligrams per deciliter as shown by the horizontal line.

As expected, based on the known effects of parathyroid hormone and on the transient exposure to teriparatide following each dose, there was a brief, transient increase in the mean serum calcium concentrations following a 20 microgram dose. The mean baseline serum calcium concentration was 2.3 millimoles per liter or 9.2 milligrams per deciliter,

and the mean peak serum calcium concentration occurred at 4.25 hours after the dose and was 2.4 millimoles per liter, or 9.6 milligrams per deciliter.

Very few patients even transiently exceeded the upper limit of normal.

Serum calcium returned to baseline by 16 to 24 hours after the dose, and the serum calcium at this endpoint was not increased in either the 20 microgram or the 40 microgram dose.

In the 20 microgram group, these transient changes in serum calcium were small. Median increase was 0.3 to 0.5 milligrams per deciliter at each study visit, and 97 percent of the patients never exceeded 11 milligrams per deciliter. The highest observed value was 11.6 milligrams per deciliter.

Eight percent of the patients had a single high serum calcium and exceeded the upper limit of normal, and three percent exceeded the upper limit of normal on two consecutive four to six-hour post dose measurements.

The transient changes in serum calcium were greater in the 40 microgram group, with a median

increase ranging from 0.5 to 0.7 milligrams per deciliter and with more patients exceeding the upper limit of normal.

Transient increases in serum calcium which exceeded the upper limit of normal were not associated with clinical adverse events in either treatment group, however.

The pre-dose serum calcium was measured 16 to 24 hours after the preceding dose in a subgroup of approximately 450 patients. This graph shows the medians and the 25th to 75th percentile range for the pre-dose serum calcium at each visit during the study. The upper and lower limits for serum calcium are shown by the horizontal lines.

There was a small decrease in the serum calcium in the placebo group at three and six months, but the pre-dose serum calcium in the teriparatide treated groups remain similar to baseline throughout the entire course of the study.

We also observed expected effects on urinary calcium excretion, which were consistent with the known physiology and pharmacology of parathyroid

hormone. The median urinary calcium excretion in the placebo group was 3.9 millimoles per day or 156 milligrams per day. There was a small increase in the 24-hour urinary calcium excretion for the first six months, and the median increase was 30 milligrams per day at the six month time point.

There was no difference among treatment groups in the number of patients with elevated urinary calcium excretion, and the highest observed 24-hour urinary calcium excretion was similar to placebo and the two teriparatide treated groups. The result showed no increase in the incidence of urolithiasis or related events.

We've shown a lot of data on the serum and urine calcium. Let me summarize those results before moving on to the remainder of the presentation.

The magnitude of the serum calcium effects were small, 0.3 to 0.5 milligrams per deciliter in the 20 microgram group, and the effects on serum calcium were brief, with the serum calcium returning to baseline after every dose.

There were small increases in the 24 hour

urinary calcium excretion. The median was 30 milligrams a day, and there were no clinical adverse events associated with the increases in the serum or urine calcium.

These data indicate that monitoring of serum in urine calcium is not necessary in patients treated with 20 micrograms a day of teriparatide.

Parathyroid hormone has known effects of uric acid clearance and effects on uric acid were also observed in our studies with teriparatide. This slide shows a dose dependent increase in the serum uric acid which was observed at one month and remained at a similar level throughout 12 months.

The serum uric acid concentration in the placebo group was 270 micromoles per liter or 4.5 milligrams per deciliter. The median increase was 0.9 milligrams per deciliter in the 20 microgram group and 1.2 milligrams per deciliter in the 40 microgram group.

The increases in serum uric acid resulted in 2.8 percent of patients in the 20 microgram group and five percent of patients in the 40 microgram

group, exceeding the upper limit of normal at least once during the study.

These increases in serum uric acid did not result in an increased incidence of gout or arthralgia, however.

There are a number of conditions that have been historically associated with hyper parathyriodism. We examined our clinical trial data to determine if these conditions were associated with teriparatide administration.

The incidence of cardiovascular disease, hypertension, peptic ulcer disease, renal insufficiency, and urolithiasis were not increased in the teriparatide treated patients.

The next few slides summarize the renal and hemodynamic evaluations in more detail. Clinical and laboratory data were examined in order to evaluate potential effects on the kidney. There was no significant effect on the incidence of urolithiasis or related terms, on serum creatinine concentrations, on measured creatinine clearance, or on routine urinalysis during the study.

Routine vital signs were obtained in the Phase 3 studies, and more extensive hemodynamic evaluations, including serial orthostatic blood pressure measurements were performed in the clinical pharmacology studies.

In the clinical pharmacology studies which enrolled health volunteers generally over age 50, we were able to detect small changes in the post dose heart rate, which were also detected as a shortening of the RR interval on the electrocardiogram. There was no QTC prolongation or other clinically significant effect on the electrocardiogram following a 20 microgram dose or any other dose study.

There were no significant effects on standing or supine blood pressure in the 20 microgram dose, although there have been occasional subjects who experience transient symptomatic postural hypotension following teriparatide administration. This was observed once following a 20 microgram dose and more frequently at higher doses. Symptoms were relieved by lying down, and they did not preclude further dosing.

A number of subject receive subsequent and

sometimes higher doses of teriparatide without experiencing orthostatic hypotension.

In the Phase 3 studies in which there were no restrictions in activity. There was not an effect on sitting blood pressure or pulse or on the incidence of postural hypotension. Nevertheless, it is possible that a patient may experience transient, symptomatic, postural hypotension following a 20 microgram dose of teriparatide.

I'd now like to describe the clinical and laboratory effects after discontinuation of treatment. These are the interim results from the ongoing follow-up study, GHBJ. Patients who had participated in any of the previous Phase 3 studies were invited to participate in the follow-up study. Approximately 80 percent of the women and men who enrolled in the prior treatment studies enrolled into Study GHBJ.

The patients have completed the first two visits, which were approximately six and 18 months after the end of the prior treatment studies. This represents a total of 39 months of cumulative observation for the women previously enrolled in the

previous Study GHAC and 30 months in the men previously enrolled in the pivotal study GHAJ.

When we first discussed the results of the patients previously enrolled in Study GHAC, at the first study visit approximately six months after the end of the treatment study, there is no longer a difference from placebo in nausea, headache, leg cramps or clinical laboratory endpoints, except for the serum uric acid.

The increase in serum uric acid concentration had declined to less than two percent, but it was still statistically significant.

The number of patients in the teriparatide treated groups with abnormal serum uric acid concentrations was no longer different from placebo. There was a small, a less than two percent, but statistically significant increase in the serum creatinine. There was no decrease in the measured serum or I'm sorry. There was no decrease in the measured creatinine clearance, and only one patient in the placebo group and one patient in the 40 microgram group had a clinically significant increase of greater

than 0.4 milligrams per deciliter.

These effects were not observed in the other Phase 3 studies.

Through visit two of the follow-up study, approximately 18 months after the end of the treatment study, there were no new clinically significant safety issues identified. There continued to be no increase in the incidence of cancer, urolithiasis, gout or arthralgia, and there continued to be a reduction in the incidence of new or worsened back pain, which is consistent with the observed continued reduction in radiographic vertebral fractures.

We also recorded non-vertebral fractures in the follow-up study, and this analysis shows the time to first non-vertebral fragility fracture for the women in Study GHAC, who were then followed in Study GHBJ. This horizontal line represents the period of time during which treatment was discontinued.

The initial part of this curve is identical to the one previously shown by Dr. Mitlak. The risk of non-vertebral fracture following discontinuation of treatment did not increase in the

teriparatide treated groups. The absolute risk reduction in teriparatide treated patients at the end of study GHAC was three percent, and the absolute risk reduction was approximately five percent at GHBJ visit two.

That concludes the presentation of the safety data in the pivotal study and the follow-up study in post menopausal women.

I'd now like to briefly review the safety evaluations in the men with osteoporosis. Study GHBJ was the pivotal study in 437 men with osteoporosis, and the results are similar to the study in post menopausal women.

This slide shows the results of the clinical and laboratory effects in the study in men. As was observed in the post menopausal women, there was a dose dependent increase in the number of patients with at least one serum calcium exceeding the upper limit of normal at four to six hours after the dose, but the number confirmed on repeat testing was only 1.3 percent in the 20 microgram group.

The magnitude and the time course of the

serum calcium was also comparable to what was shown in the post menopausal women.

There was a significant increase in nausea and headache at the 40 microgram group, but not the 20 microgram group.

There was no trend towards increase in leg cramps in the men. However, there were too few events in this study to evaluate that effect adequately.

There was also a significant increase in the number of men, again, in the 40 microgram group, but not the 20 microgram group who discontinued due to adverse event, and just as was the case in the post menopausal women, the discontinuation in the 40 microgram group were largely attributable to nausea.

The other clinical and laboratory effects, such as effects on serum urine calcium and urinary calcium excretion were also comparable to the effects in post menopausal women.

We also performed pharmacokinetic measurements in the men. The time to peak concentration and the apparent elimination half-life were similar in men and women, but the serum

concentrations of teriparatide were 20 to 30 percent lower in men than in women.

As Dr. Mitlak and I have described, the effects on spine and hip bone mineral density, clinical adverse effects, and laboratory tests were similar in men and women.

Well, not an endpoint in Study GHAJ, spine radiographs were obtained as a screening test and follow-up spine radiographs were obtained at visit two of the follow-up study of GHBJ in order to provide a more complete set of data with which to compare to the women.

This slide shows the vertebral fracture incidence in men and the time between the baseline and follow-up radiographs includes both the treatment and follow-up phase, a total of 30 months.

There were fewer fractures in this study than in the pivotal study in post menopausal women, and there were too few fractures to have adequate statistical power.

Nevertheless, the observed patterns in vertebral fractures in the men and in moderate and

severe vertebral fractures in the men was similar to the patterns observed in the post menopausal women.

In addition, the number of men sustaining new vertebral fractures or new moderate to severe vertebral fractures was identical in the 20 and 40 microgram groups.

While this analysis is not a pre-specified analysis of the study, it does illustrate the similarity of the similarity of the response to treatment in men and in women, and it supports the 20 micrograms as the appropriate dose in men as well as in women.

In addition to examining potential gender differences, we also examined special populations based on age, renal function, cardiac function and blood pressure. There were no clinically significant pharmacokinetic or safety findings in these special populations, and restrictions or special monitoring of patients with these conditions are not necessary.

We also performed clinical pharmacology studies which evaluated potential pharmacodynamic and safety interactions with hydrochlorothiazide,

furosemide, calcium channel blockers, Atenolol, Digoxin, hormone replacement therapy, and Raloxifene. There were no clinically significant interactions with teriparatide in these drug interaction studies, and restrictions or special monitoring of patients taking these medications was also not necessary.

Now, let me conclude by summarizing the results of the clinical and safety evaluations of teriparatide. In the Phase 3 studies, leg cramps and possibly nausea were treatment related at the 20 microgram dose.

Forty micrograms per day was more likely to cause nausea, headache and discontinuation due to adverse events.

The increased incidence of symptomatic postural hypotension observed in the clinical pharmacology studies was not observed in the Phase 3 studies.

Finally, there was a lower incidence of back pain in both the 20 and 40 microgram groups, which was consistent with the reduction in vertebral fractures.

The laboratory evaluations showed the expected transient effects on serum calcium, and the expected pharmacologic effects on serum uric acid and on urinary calcium excretion. These effects were small and were not associated with clinical adverse effects, and 40 micrograms a day was more likely to causae increased serum calcium and serum uric acid.

After discontinuation of treatment, nausea, headache, leg cramps, and the laboratory effects quickly resolved, except for the small increase in serum uric acid. Through 18 months of post treatment follow-up no new clinically significant adverse effects were identified, and there continued to be no increase in the incidence of cancer, urolithiasis, gout or arthralgia, and there was no increase in the rate of nonvertebral fractures.

There continued to be a continued significant reduction in the incidence of new or worsened back pain.

In conclusion, teriparatide 20 micrograms and 40 micrograms a day were safe and well tolerated in our studies of treatment of post menopausal women

and men with osteoporosis. The effects on the clinical laboratory tests were small and consistent with the known physiology and pharmacology of parathyroid hormone, and routine laboratory monitoring in patients taking 20 micrograms a day is not necessary.

Likewise, restrictions or monitoring in the special population study are not necessary. There were no significant drug interactions identified, and finally, although both doses were safe, teriparatide 20 micrograms a day was associated with fewer adverse effects.

I thank you very much for your attention, and Dr. Mitlak will conclude this morning's presentations with the summary and conclusions.

DR. MITLAK: Mr. Chairman, members of the committee, I have the pleasure of concluding the formal presentation from Lilly this morning.

We've provided evidence for you that teriparatide is a bone forming agent that increases bone mineral density, improves bone microarchitecture, and prevents fractures in patients with osteoporosis.

Teriparatide was safe and well tolerated by patients in the clinical trials.

To summarize the presentations, Dr. Lindsay outlined the pressing clinical need for such an agent and reviewed the breadth of prior experience with teriparatide.

Dr. Vahle presented nonclinical data demonstrating that teriparatide is a bone forming agent that increases bone mass and strength in several species. He also described the finding of osteosarcoma in a long-term study in rats and outlined factors that are important in understanding the relevance of the findings to the proposed use in women and men with osteoporosis.

Dr. Gaich and I presented the favorable overall clinical profile for teriparatide.

Let me begin now by reviewing our considerations on the nonclinical findings. In 1999, the following experts were convened to review the findings in the nonclinical study and to provide advice on the follow-up of study participants. These include Drs. Chabner, Adamson, Antman, Henderson,

Fletcher, Raymond, Kronenberg, and Doppelt. Drs. Chabner and Adamson are in attendance with us today.

This PTH oncology board reviewed the available nonclinical and clinical data and provided the following conclusions for us.

Based on current information, the findings in the rat study were unlikely to predict for the development of bone tumors in patients who had received teriparatide in the clinical trials. This conclusion was reached with considerations of the following:

The lifetime duration of treatment in the rats compared with a relatively brief exposure intended in humans;

The fact that treatment was initiated during the rapid growth phase of the animals;

The difference in rat and human bone biology and response to PTH;

And the lack of clinical association between hyperparathyroidism and osteosarcoma in humans.

Since then we have evaluated additional

nonclinical and clinical information and have had ongoing discussions with our consultants and with the agency. In specific, as described by Dr. Vahle, no skeletal lesions were observed in an 18-month study in monkeys given four to eight times the exposure of subjects in the Phase 3 trial.

While we recognize that there are temporal differences in the profile of PTH exposure in patients with hyperparathyroidism and those who had received teriparatide as treatment for osteoporosis, osteoblast stimulation occurs in both, often to a greater extent in patients with hyperparathyroidism, and patients with hyperparathyroidism can have elevated levels of parathyroid hormone for years.

New bone formation also occurs in patients with hyperparathyroidism, but resorption usually occurs to a greater degree.

We identified a single case report of the co-occurrence of hyperparathyroidism and osteosarcoma in the literature. Dr. Olaf Unell (phonetic) then assisted us by performing a systematic search of the national cancer registry in Sweden which covers the

entire population and 40 years of exposure. We were able to identify 12,644 patients who had been identified as either having a parathyroid adenoma or parathyroid hyperplasia and linked this to the cancer registry.

There was no case where the diagnosis of hyperparathyroidism and osteosarcoma occurred in the same patient.

As previously described also, Study GHBJ, the observational study, was designed with input from the oncology board and to date has provided approximately 2,000 additional patient-years of follow-up. No primary bone tumors have been reported in any patient.

We've concluded that it is unlikely that the findings in the long-term study in rats predict a risk for bone tumors in patients who had received teriparatide for treatment of osteoporosis.

We have promptly shared information about the animal findings with the scientific community and with the regulatory agencies. We reported the rodent findings in clinical presentations, the initial

presentations given at the Endocrine Society by Dr. Neer, at the American Society of Bone and Mineral Research by Dr. Marcus, and the American College of Rheumatology by Dr. Gennant, and it included information about the animal findings in many subsequent presentations.

We have also included a description of the animal findings in the primary publication of the study data.

The GHBJ study was also designed to collect some additional safety information, but also to facilitate information sharing and, therefore, we had set the study up to maintain contact between the physicians and our prior study patients.

Now, looking forward, we would propose to exclude groups that increased risk for osteosarcoma, such as those with Paget's disease, unexplained elevations of alkaline phosphatase, adolescents or those with open epiphoces (phonetic), and those with a history of radiation to increase the certainty with which we can begin to exclude or further exclude a relationship with teriparatide treatment over time.

To insure the most favorable benefit-risk for this important potential therapy for patients with osteoporosis, we also proposed to limit the duration of treatment for up to two years in post menopausal women and men based on currently available data.

We continue to put patient safety first and provide a commitment to the following elements of a post approval safety surveillance program. Lilly has a worldwide system for assessing spontaneous adverse reports that is already in place to collect information on men and women who did not elect to participate in Study GHBJ. This system will be used to track safety in a post approval setting.

We will continue long-term follow-up of women and men in Study GHBJ, and by 2005, we'll have accrued approximately 7,000 patient-years of follow-up on these subjects.

We are working with the agency to create an active program with a goal of collecting and assessing information on a substantial proportion of cases of osteosarcoma that occur in the United States each year regardless of any treatment they may have

received.

Because of the very low incidence of this disorder, we propose to utilize large, stable, population based databases, such as the NCI's SEER database, and also to work with sentinel sites, that is, specialty referral centers where such patients with the disorder receive care.

We will provide a periodic update on prescriptions by geographic region to the agency. We will work and review new information on a periodic basis with an external safety review board. This program will be ready to be implemented at launch.

Now, to summarize the clinical data. Teriparatide treatment improves skeletal architecture. These CT scans of baseline and follow-up iliac crest bone biopsy from a patient treated with teriparatide provides evidence for enhanced architecture, that is, improvement in the trabecular network of bone from the baseline state to the follow-up state after treatment. It is data similar to that which was shown earlier this morning by Dr. Lindsay.

This effect of teriparatide was associated

with significant favorable effects on clinical outcomes on study patients, that is, treatment prevented fractures.

We have considered the following in dose selection. In the Phase 3 trial, vertebral and nonvertebral fracture risk was reduced to a similar extent in the 20 and 40 microgram groups in women. While there was a rapid and dose related increase in the surrogate outcome of bone density at the spine and hip in women and men, the actual increase in spine and femoral neck and total hip bone density was similar for women and men.

The 40 microgram dose was more likely to cause adverse events, transient elevations in serum calcium, and resulted in a higher rate of discontinuations from the trials in women and in men.

Teriparatide 20 micrograms is an appropriate dose for treatment of osteoporosis in post menopausal women and in men.

Pharmacokinetic and pharmacodynamic analyses supported that dose adjustment is not required for gender, weight or age.

To summarize the effect of teriparatide 20 micrograms, in women in Study GHAC, teriparatide 20 micrograms reduced the risk of vertebral fracture by 65 percent; reduced the risk of nonvertebral fractures by 53 percent; increased bone mineral density at the spine and hip without a significant effect at the forearm; and increased total body bone mineral. There was no increase in fracture risk for at least 18 months after cessation of treatment.

In the study in men, teriparatide significantly increased bone mineral density at the spine and femoral neck without significant effect at the total hip, and there was a significant increase in total body bone mineral.

The adverse effects associated with teriparatide treatment in the Phase 3 clinical trials in women were nausea and leg cramps. The overall pattern was similar in men, except for that leg cramps were not reported at an increased frequency.

In the clinical pharmacology studies, postural hypotension was observed, but almost always after doses of 40 micrograms or greater.

While the incidence of clinical apparent postural hypotension was not different among groups in the Phase 3 trials, we believe that this is a potential treatment related effect.

We observed increases in serum calcium between four to six hours post dose that had returned to baseline by 16 hours post dose. The levels transiently exceeded the normal range of repeat in only about three percent of women, and there was no difference from baseline in pre-dose serum calcium at any visit.

There was a median increase in serum uric acid of about 20 percent without effect on the incidence of gout or arthralgia.

There was no increase in the risk of cancer, no primary bone tumors were reported, and there was no effect on mortality.

Teriparatide treatment restores bone architecture and bone mass. No other osteoporosis treatment can do this. The now demonstrated ability to prevent fractures confirms that teriparatide can fulfill an important unmet medical need in women and

in men with osteoporosis.

Clinical trials support that 20 micrograms per day is an effective and safe treatment for osteoporosis in post menopausal women and in men.

This now concludes the presentation from Lilly. Thank you very much for your attention.

ACTING CHAIRMAN MOLITCH: I'd like to thank the sponsor for a crisp presentation that came in on time.

We now have the opportunity for the panel to ask questions of the sponsor. At this point we'd like to try to ask questions that are specifically related to the presentation, the data presented, as far as factual questions regarding this.

I think additional philosophical questions and other types of things we'll have the opportunity to discuss later.

So if any members of the panel would like to start with questioning, please do.

Dr. Bone.

DR. BONE: Thank you.

I appreciate your very nice presentation.

I have one or two -- actually I have several questions, but I'll try to ask them one or two at a time.

With regard to the osteosarcomas, when you investigated the animal tumors, what did you find out about their responsiveness to parathyroid hormone? Do they have receptors? Do they respond in vitro to parathyroid hormone? Are these tumors ones that may have been a result of an effect on early differentiation but no ongoing effect of the tumor by the hormone or is it something that's stimulated as we go along?

DR. MITLAK: Let me invite our toxicologist, Dr. Vahle, to response.

DR. VAHLE: We've not isolated the osteosarcoma cells in vitro to study PTH receptor density or responsiveness to teriparatide. So we don't have any direct evidence to address your question one way or the other.

DR. BONE: Was the receptor expressed in the tissue, in the slides?

DR. VAHLE: We've not done any receptor

identification in those specific slides or have grown them in culture either.

DR. BONE: Why?

DR. VAHLE: Because there are technical difficulties in getting to that PTH receptor in those specific slides. Also, in investigating that, it was not clear whether that was going to give us clear information about their relevance to humans.

DR. BONE: I'm a little disappointed that you didn't look.

Okay. I have a couple more questions if nobody else has one right now. Okay.

Could you show us the nonvertebral fracture data in men, the actual data?

DR. MITLAK: Well, the actual data are that there were six nonvertebral fractures in the male study, three in placebo, two in the 20 microgram dose group, and one in the 40 microgram dose group. Is that sufficient?

DR. BONE: Okay. Where were the fractures? What sites? Were they hip fractures?

DR. MITLAK: No, they were not hip

fractures.

DR. BONE: None of them?

DR. MITLAK: None of them.

ACTING CHAIRPERSON MOLITCH: Dr. Levitsky.

DR. LEVITSKY: Do you have any data or can you summarize data on the serial or concomitant use of bisphosphonates with this agent?

DR. MITLAK: I'm sorry?

DR. LEVITSKY: Do you have any data on the serial or concomitant use of bisphosphonates with this agent?

DR. MITLAK: We have just limited data to share with you on this. Let me ask for slide 4261.

What this slide shows is information from the 58 patients who had reported prior use of bisphosphonate prior to enrollment in the study. Because the study began enrolling in 1995 and '96, the bisphosphonates that were more commonly used and were available included primarily atidronate. There were also a few patients who received alendronate or toludrinate, and in one patient who received abandronate.

These data show that compared with placebo, the overall change in bone density was similar to the larger population. I do not have a lot of information on precisely how long the patients used these, but they had stopped treatment for between six and 24 months prior to enrollment in the study.

DR. KREISBERG: I also have several questions. I'd like to ask whether you conducted any studies in orchiectomised (phonetic) male primates. I didn't understand from the presentation in your experimental models whether the male primates were androgen deficient or not

DR. MITLAK: Dr. Vahle, please.

DR. VAHLE: Consistent with the guidances, the 18-month pharmacology study I described was limited to ovariectomized females. So we have not studied the similar model in males.

DR. KREISBERG: The other question that is partially related to that is whether in the human studies, where you were treating hypergonadal men and men with idiopathic osteoporosis, whether the hypergonadal men also received androgen replacement.

DR. MITLAK: The study in men included approximately half of the men that had idiopathic osteoporosis and half were hypergonadal. Testosterone treatment, if it was being used by men, could be continued during the study, but was not permitted to be started de novo during the study.

A small proportion of men, in the range of ten percent or less, had been taking testosterone or an androgen replacement into the study, and as we said, overall the response in men with idiopathic and hypogonadal osteoporosis to teriparatide treatment was similar.

ACTING CHAIRPERSON MOLITCH: Dr. Aoki.

DR. AOKI: Do you have any data or are you planning any studies on monkeys older, for periods longer than 18 months, or on rats that are older than six to eight weeks to determine if the osteosarcoma is, in fact, somehow age related in the rats and to see the more relevant model, whether or not the osteosarcoma question can be laid to rest using longer term studies?

DR. MITLAK: Let me ask Dr. Vahle again to

comment on the work that's ongoing.

DR. VAHLE: Since the initial observation, we've worked closely with our experts as well as the FDA in developing some ongoing research that I'd be happy to share with you.

If I could please have slide 4222, let me briefly highlight the two main components of this.

First, in response to the second portion of your question, yes, we are conducting a follow-up rat study which looks at two things: one, the effect of treatment duration and, two, the effect of age at treatment initiation.

In this respect it addresses the question. We have treatment arms which avoid the phase of rapid skeletal growth, and this is a study that was conducted or designed in collaboration with the agency as a Phase 4 commitment.

In terms of additional monkey work, what we are doing is an additional study which has an 18-month treatment period. This represents approximately eight percent of the monkey's lifetime at exposures up to eightfold human exposures, but it contrasts with

our prior work in that it's followed by a minimum three year observation period to allow us to have some extended follow-up data in the primate model, and again, this is a study that we are in the early stages of and designed with the agency.

DR. BONE: Going back to the series of questions, could you discuss what studies you are conducting concerning the -- or have conducted -- concerning the mechanism by which these osteosarcomas were induced, biological mechanism?

DR. VAHLE: As part of that ongoing research program, another component of that was to convene a group to try to discern what type of mechanistic studies would be useful in trying to assess the relevance to humans, and again, this is something that we have discussed with the division.

It has not been clear that there are a direct set of experiments that will help us understand the mechanism in the rat and then clearly differentiate it from the humans at a cellular or molecular level. Rather, we have focused on these effects of treatment duration and age of initiation

because it's clear these differences between the rat model and the human that we want to more clearly establish.

In those follow-up studies, we are continuing to evaluate new technologies, such as gene array or genetic characterization to see if they would provide any assistance or any additional insight.

DR. BONE: Have you completed any studies addressing this mechanism at all?

DR. VAHLE: No, there have been no studies completed to date. The studies and the concepts I've outlined are all in progress. What I can share though is interim results from the long-term rat study, and that following six months' treatment duration, both during the rapid phase of skeletal growth as well as after the rapid phase of skeletal growth, there are no bone proliferative lesions, and there are the anticipated exaggerated effects on the skeleton, but again, that study is still in progress.

DR. GRADY: I'd like to ask a little bit about nephrotoxicity. It seemed that in one of your monkey studies at least there was a fair percentage of

the animals who had nephropathy, and one out of eight in that study with renal failure, and I don't think you talked about that at all.

DR. MITLAK: Please.

DR. VAHLE: I'd certainly be happy to address the renal findings.

If I could go back to the main slide 28, please, we've studied renal tissue and renal function in two different models. In the toxicity studies, and there are a group of three different toxicology studies represented here, we observed these subtle histologic observations in the kidneys of monkeys over a range of doses and over a range of duration of exposure, both three-month studies and up to one year.

We conducted -- because in those routine studies there was no clear evidence that these renal changes had an impact on renal function, we conducted a special study to determine if these changes had effects on renal function.

That study was conducted at a high dose of 40 micrograms per kilogram. That provides exposures that are in excess of 100-fold what a woman would